Paracetamol decreases steady-state exposure to lamotrigine by induction of glucuronidation in healthy subjects

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WHAT IS KNOWN ABOUT THIS SUBJECT

- A clinical trial from 1990 revealed that multiple doses of paracetamol decrease the total systemic exposure of a single dose of lamotrigine by 20%.
- Decision-support recommendations on concomitant use of these drugs are contradictory.

WHAT THIS STUDY ADDS

- The clinically relevant steady-state systemic exposure (AUC) of lamotrigine is decreased by 20% and plasma trough values by 25% during concomitant treatment with paracetamol due to an induction of the glucuronidation pathways.
- Patients with plasma concentrations of lamotrigine at the lower end of the therapeutic range may be susceptible to a clinically relevant interaction with paracetamol.

AIM

Patients receiving lamotrigine therapy frequently use paracetamol concomitantly. While one study suggests a possible, clinically relevant drug–drug interaction, practical recommendations of the concomitant use are inconsistent. We performed a systematic pharmacokinetic study in healthy volunteers to quantify the effect of 4 day treatment with paracetamol on the metabolism of steady-state lamotrigine.

METHODS

Twelve healthy, male volunteers participated in an open label, sequential interaction study. Lamotrigine was titrated to steady-state (100 mg daily) over 36 days, and blood and urine sampling was performed in a non-randomized order with and without paracetamol (1 g four times daily). The primary endpoint was change in steady-state area under the plasma concentration–time curve of lamotrigine. Secondary endpoints were changes in total apparent oral clearance, renal clearance, trough concentration of lamotrigine and formation clearance of lamotrigine glucuronide conjugates.

RESULTS

Co-administration of lamotrigine and paracetamol decreased the steady-state area under the plasma concentration–time curve of lamotrigine by 20% (95% CI 10%, 25%; $P < 0.001$) from 166 to 127 μmol l^{-1}. Concomitant administration of paracetamol increased the formation clearance of lamotrigine glucuronide conjugates by 45% (95% CI 18%, 79%, $P = 0.005$) from 1.7 to 2.8 l h^{-1}, while the trough value of lamotrigine was reduced by 25% (95% CI 12%, 36%, $P = 0.003$) from 5.3 to 3.9 μmol l^{-1}.

CONCLUSION

Paracetamol statistically significantly induced steady-state lamotrigine glucuronidation, resulting in a 20% decrease in total systemic exposure and a 25% decrease in trough value of lamotrigine. This interaction may be of clinical relevance in some patients.

Introduction

Lamotrigine is an anti-epileptic drug (AED) used worldwide in the treatment of epilepsy and bipolar disorder [1]. It is often considered the first choice treatment for elderly people and women of childbearing age because of its favourable tolerability profile [2]. Most AEDs have a narrow therapeutic index and drug interactions with AEDs may easily result in toxicity or seizure breakthrough [2]. Back in 1990, Depot *et al.* [3] investigated the effect of multiple doses of paracetamol, 900 mg three times daily for 11 days, on the pharmacokinetics of a single dose of lamotrigine, 300 mg, in healthy male volunteers. The total systemic exposure of lamotrigine decreased by 20% and the elimination half-life by 15%, which indicated a facilitation of lamotrigine removal and not the inhibition the study was designed to investigate. The design of the study with a single dose of lamotrigine with and without exposure to steady-state paracetamol differs from the practical use of lamotrigine. Nevertheless, the effect of this study has caused different interpretations of the clinical consequences of concomitant use of lamotrigine and paracetamol, and has left physicians with contradictory practical recommendations [4, 5]. The two most used and appraised decision-support systems among health-care professionals on drug–drug interactions thus offer ambiguous interpretation and practical advice: Micromedex state: '*Concurrent use of lamotrigine and acetaminophen (paracetamol) may result in decreased lamotrigine effectiveness*'. [4]. Stockley's Drug Interactions state: '*It is unlikely that this reduction in lamotrigine exposure is of clinical importance*' [5].

Lamotrigine is metabolized (80%) to inactive metabolites [6], mainly 2-N-glucuronide conjugates, which are eliminated in the urine [6, 7]. The metabolism of lamotrigine is inhibited by sodium valproate (VPA) and induced by other AEDs and oral contraceptives [8]. These drug–drug interactions are presumably caused by an inhibition or induction of uridine diphosphate (UDP) glucuronosyltransferases (UGTs), which catalyze the glucuronidation of lamotrigine [6, 9]. If lamotrigine is combined with the above-mentioned drugs, the maintenance dose should be altered to avoid adverse events or sub-therapeutic plasma concentrations [6, 10, 11]. Paracetamol (acetaminophen) which is an analgesic and antipyretic over-the-counter drug used worldwide is also mainly metabolized by glucuronidation (50%) [6]. Therefore, when lamotrigine and paracetamol are administered simultaneously, it is biologically plausible that competitive inhibition of the UGTs will result in increased exposure of either drug.

The extrapolation of the results from Depot *et al.* [3] to clinical practice is difficult, because patients receiving lamotrigine will be at steady-state, and concomitant paracetamol treatment will usually be 1 g four times daily. The aim of this study was to clarify the potential inhibitory effect of standard dose paracetamol 1 g four times daily on the metabolism of steady-state lamotrigine in healthy male volunteers.

Methods

Design

This was an open label, sequential interaction study in 12 healthy male volunteers.

Study participants

Study participants were recruited through posters at the University of Southern Denmark. The inclusion criteria were men aged 18–64 years with normal liver and kidney function, as assessed by estimated glomerular filtration rate (eGFR), alanine aminotransferase, bilirubin, albumin and coagulation factors II, VII and X. The exclusion criteria were intake of prescription medication, over-the-counter drugs, herbal medicine or dietary supplements and/or hypersensitivity to lamotrigine and/or paracetamol. The participants were not allowed to consume alcohol at an amount that exceeded 14 units per week in accordance with the recommendation from the Danish Health and Medicines Authority [12]. During the sampling period, the participants were not allowed to consume any alcohol.

Approvals

All participants gave written informed consent to participate in the study. The research protocol received prior approval by The Danish Health and Medicines Authority (J. no: 2 014 081 192), The Scientific Ethical Committee (J. no.: S-20 140 143) and The Danish Data Protection Agency (14/41 540). The trial was registered in the US National Institute of Health register (www.clinicaltrials.gov) (identifier NCT02303106). The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice (GCP), and monitored by the GCP unit, Odense University Hospital (Odense, Denmark).

Study medication

The daily dose of lamotrigine (Lamictal® GlaxoSmithKline Pharma A/S, Denmark) was administered once daily at 08.00 h. The participants began with lamotrigine 25 mg once daily in the first 2 weeks (days 1–14). The dose was increased to 50 mg once daily in the third and fourth week (days 15–28). On the first day in the fifth week (day 29), the dose was increased to the target dose of 100 mg once daily for the rest of the study period (days 29–40). From day 37 to day 40, 1 g paracetamol (Pinex® Actavis A/S, Denmark) was administered four times daily and the first dose was taken at 08.00 h (together with lamotrigine) and the last dose at 20.00 h.

Blood and urine sampling

Blood and urine were sampled on day 36 and day 40. Blood samples were drawn 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12 and 24 h after the daily intake at 08.00 h. Urine was collected simultaneously for 24 h. On day 37, the initial dose of paracetamol was administered immediately after the last blood sample was drawn (08.00 h), and the participants continued the intake of paracetamol 1 g four times daily for the next 3 days. The second blood and urine sampling took place on day 40 with identical sampling. One blood sample was drawn to control for compliance of paracetamol at 08.00 h on day 40.

Analytical methods

The plasma and urine concentrations of lamotrigine were determined using a validated high performance liquid chromatography method with a limit of quantification of 0.45 μmol l^{-1} and a coefficient of variation of 5%. Briefly, lamotrigine was extracted by liquid–liquid extraction. A 100 μl sample was added using 20 μl internal standard (ethyl-buthyl babuturic acid) solution and 2 ml of ethylacetate : heptane solution (50 : 50 v/v) and vortexed for 5 min. The organic phase was collected and evaporated to dryness by dry nitrogen. Lamotrigine was reconstituted in 150 μl mobile phase (0.1% aqueous formic acid : 0.1% formic acid in methanol (70 : 30 v/v)). Injection volume was 20 μl using an Agilent Poroschell 120 EC-C18 2,7 μm 3.0 × 50 mm column and lamotrigine was detected by u.v. absorption at 220 nm.

The concentration of lamotrigine in urine was measured before and after the addition of β-glucuronidase enzyme to the urine. β-glucuronidase enzyme was added and the urine was incubated for a period of 20 h. The concentration of lamotrigine glucuronides in urine was calculated as the difference between the second and the first measurement of the concentration of lamotrigine in urine.

Plasma concentrations of paracetamol were measured using a validated spectrophotometry-based method with a limit of quantification of 0.02 mmol l^{-1} and a coefficient of variation of 2%. Briefly, paracetamol is cleaved to p-aminophenol and acetate when aryl-acylamidase is added. When adding 8-hydroxyquinolin-5-sulfonic acid and manganese ions, the coloured substance 5-(4-iminophenol)-8-quinolone is formed. The increase in absorbance at 615 nm is caused by the formation of the 5-(4-iminophenol)-8-quinolone and it is proportional to the sample concentration of paracetamol.

Pharmacokinetic data analysis

The pharmacokinetic parameters were calculated by non-compartmental methods using the software package WinNonlin Professional, version 6.3 (Pharsight, Mountain View, CA, USA). The AUC(0,24 h) of lamotrigine was calculated using the linear-up log-down method. The peak values of maximum plasma concentration

(C_{max}) and time to the maximal plasma concentration (t_{max}) were obtained directly from the observed data.

The renal clearance of lamotrigine (CL_{renal}) was calculated as:

$$CL_{renal} = \frac{\text{amount of LTG in urine}_{0,24\ h}}{AUC_{0,24\ h}}$$

The formation clearance of lamotrigine glucuronides was calculated as:

$$CL_f = \frac{\text{Total amount of NLTG in urine } (0,24\ h)}{AUC_{LTG\ (0,24\ h)}}$$

Lamotrigine glucuronides are not further metabolized and are excreted in the urine [8].

Statistical analysis

To detect a true increase of 20% in lamotrigine AUC(0,24 h), a total of 10 participants were required in a crossover design assuming a two-sided level of significance of 0.05 and a power of 80%. To allow for a dropout rate of 20%, 12 subjects were included.

Descriptive data are presented as medians and ranges. Inferential analyses of pharmacokinetic data are presented as geometric mean ratios with 95% confidence intervals (CI). Statistical inference was analyzed by a paired t-test on log-transformed data, except for t_{max} which was analyzed using the Wilcoxon signed-rank test. A two-sided P value less than 0.05 was considered statistically significant. Calculations and statistical analyses were performed using STATA 13 (StataCorp, TX, USA).

Results

Ten of 12 included participants completed the study. Two withdrew from the study due to adverse events. One withdrew due to intense headache, reduced appetite, sleep disturbance, vomiting and weakness shortly after the initial daily dose of 25 mg lamotrigine. The other participant withdrew due to tiredness, itchy skin rash on upper extremities as well as flushing and shivering. One participant experienced a mild headache and a swollen lymph node on the right side of the neck, but did not withdraw from the study as the symptoms eased through the study period. Full urine samples were available for seven participants. The median age of the participants was 25 years ranging from 22 to 32 years with a median body mass index of 22 kg m^{-2} ranging from 20 to 28 kg m^{-2}.

Principal pharmacokinetic parameters are listed in Table 1. Paracetamol decreased area under the curve of plasma concentration–time of lamotrigine (AUC(0,24 h)) by 20% (95% CI 10%, 25%, $P < 0.001$) (Figure 1 and

Table 1

Steady-state pharmacokinetic parameters of lamotrigine before and after administration of paracetamol

Parameter	Period 1		Period 2		GMR		
	Median	[Range]	Median	[Range]	(95% CI)		P
$AUC(0,24\ h)$ ($\mu mol\ l^{-1}h$)	166	[105–321]	127	[88–286]	0.82	(0.75, 0.90)	<0.001
CL/F ($l\ h^{-1}$)	2.4	[1.2–3.7]	3.1	[1.4–4.4]	1.22	(1.11, 1.34)	<0.001
CL_{renal} ($l\ h^{-1}$)	0.15	[0.06–0.44]	0.20	[0.11–0.38]	1.22	(0.88, 1.70)	0.19
CL_f ($l\ h^{-1}$)	1.7	[1.0–2.9]	2.8	[1.1–3.2]	1.45	(1.18, 1.79)	0.005
C_{max} ($\mu mol\ l^{-1}$)	10.1	[7.9–32.4]	9.0	[6.2–40.1]	0.97	(0.72, 1.29)	0.79
$C_{ss,min}$ ($\mu mol\ l^{-1}$)	5.3	[3.6–10.0]	3.9	[2.2–9.0]	0.75	(0.64, 0.88)	0.003
t_{max} (h)	1.8	[0.5–4.0]	1.8	[0.5–3.5]	-	-	0.96*
$Ae_{LTG,0,24\ h}$ (μmol)	25.5	[10.9–48.0]	27.4	[17.1–54.1]	1.03	(0.78, 1.35)	0.83
$Ae_{N-LTG,0,24\ h}$ (μmol)	294	[226–322]	345	[303–400]	1.22	(1.01, 1.45)	0.04

Period 1: Before paracetamol; Period 2: After paracetamol. Pharmacokinetic parameters obtained from 10 healthy volunteers. All data are presented as medians and ranges ([minimum–maximum]) with geometric mean ratios and 95% confidence intervals, except for t_{max}. Paired t-test was used as statistical test to determine significance. *The effect on t_{max} was analyzed using the non-parametric Wilcoxon signed-rank test. All pharmacokinetic parameters are calculated from steady-state plasma concentrations of lamotrigine. $AUC(0,24\ h)$, area under the steady-state curve of plasma concentration–time of lamotrigine; CL/F, apparent total clearance at steady-state after oral administration of lamotrigine; CL_{renal}, renal clearance; CL_f, formation clearance of lamotrigine glucuronides; C_{max}, maximum plasma concentration; $C_{ss,min}$, trough value of lamotrigine plasma concentration; t_{max}, time to the maximum plasma concentration; $Ae_{LTG,0,24\ h}$, total amount of lamotrigine excreted in urine in 24 h; $Ae_{N-LTG,0,24\ h}$, total amount of lamotrigine glucuronides excreted in urine in 24 h.
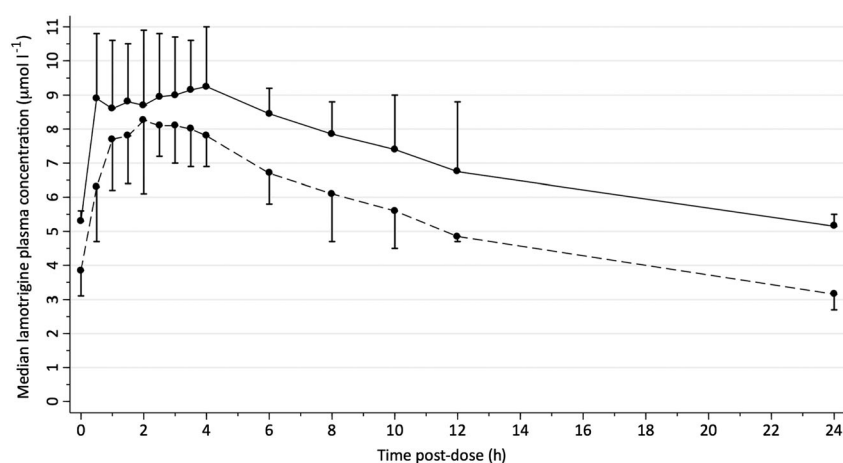
Figure 1

Median lamotrigine steady-state plasma concentration over time with (– –•– –) and without (——•——) exposure to paracetamol based on 10 volunteers

Figure 2), and the trough value of lamotrigine plasma concentration ($C_{ss,min}$) by 25% (95% CI 12%, 36%, $P = 0.003$). The formation clearance of lamotrigine glucuronides (CL_f) was increased by 45% (95% CI 18%, 79%, $P = 0.005$) (Figure 3).

Study drug compliance was measured by (i) the MARS-5 score [13], (ii) counting the returned tablets and (iii) plasma concentration measurements of paracetamol. All participants had paracetamol plasma concentrations near the limit of detectability and two of the participants had undetectable plasma concentrations. Considering the short elimination half-life of paracetamol (1–3 h [14]), it is plausible that the plasma concentration was below the level of quantification despite compliance. All 10 participants scored more than 20 points in the

MARS-5 score (<20 points indicates poor compliance) [13] and confirmed paracetamol intake according to protocol. Returned tablets of both paracetamol and lamotrigine were in accordance with the expected amount. A sensitivity analysis without the two participants with undetectable plasma concentrations of paracetamol only slightly increased the impact of paracetamol on the pharmacokinetics of lamotrigine (data not shown).

Discussion

This is the first systematic study to assess the effect of multiple doses of paracetamol on steady-state pharmacokinetics of lamotrigine in a design relevant to everyday
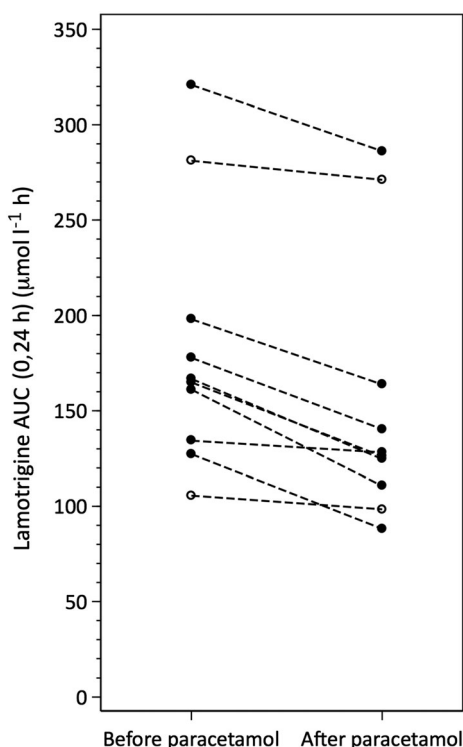
Figure 2

Lamotrigine area under the plasma concentration–time curve of 10 volunteers with and without exposure to paracetamol. Participants with undetectable paracetamol concentrations are marked with open circles
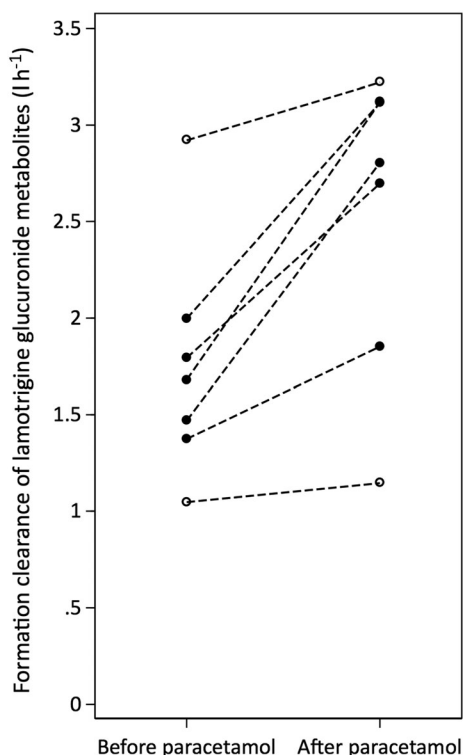

Figure 3

Formation clearance of lamotrigine glucuronides of seven volunteers with and without exposure to paracetamol. Participants with undetectable paracetamol concentrations are marked with open circles

clinical use. We demonstrate a statistically significant decrease in total systemic exposure of lamotrigine by 20 and 25% for AUC and trough concentration (C_{min}), respectively. We found a 22% increase in apparent oral total clearance at steady-state. A statistically significant 45% increase in the formation clearance of lamotrigine glucuronides (Figure 3) strongly suggests an induction of the glucuronidation pathways involved in the metabolism of lamotrigine. Hereby, we confirm the findings from the single dose study by Depot et al. [3] in a steady-state setting.

Both lamotrigine and paracetamol are substrates for the UGTs [14, 15]. N-glucuronidation accounts for approximately 80% of lamotrigine clearance [6]. In vitro studies have shown that UGT1A3, UGT1A4 and UGT2B7 are involved in the metabolism of lamotrigine, with UGT1A4 being the principal catalyst [16–18], while UGT1A1, UGT1A6, UGT1A9 and UGT2B15 are involved in the metabolism of paracetamol [8, 18].

Some disagreement about the ability of lamotrigine to induce its own metabolism exists [1, 7, 15]. Although changes in pharmacokinetic parameters in the case of an autoinduction follow the same patterns as our results, it appears unlikely that this is an issue in the current design. Following a dose-escalating period of 36 days, such an autoinductive effect would have been fully materialized.

Our study has some limitations. The study was unblinded and non-randomized. Blinding is unlikely to be of meaningful relevance as outcome measures are solely objective measurements of concentrations in plasma and urine. Sequence randomization was unfeasible due to the long dose escalation period necessary to reach steady-state while protecting healthy volunteers from adverse reactions. Hence, while unlikely, a possible period effect cannot be excluded. Our study was designed to detect the biologically most plausible mechanism; i.e. inhibition of lamotrigine metabolism by paracetamol. As paracetamol was administered for 4 days, we may have underestimated the full inductive effect. In Denmark, the recommended maintenance dose of lamotrigine in monotherapy is between 100 and 300 mg daily, but can be as high as 500–1200 mg daily [19]. Extrapolation from the studied population to the everyday clinical heterogeneous patient population presenting a wide demographic range, co-medications and co-morbidities should be made with appropriate caution.

The primary strength of our study is the clinically relevant steady-state of lamotrigine and the measurement of formation clearance of lamotrigine glucuronides. The study design reflects clinical use and provides inference estimates relevant to everyday clinical settings. Our findings are supported by measurement of the rate of formation of the glucuronide metabolites strongly supporting a biological rationale for the observations. Our results were robust to sensitivity analysis excluding participants

with undetectable plasma concentrations of paracetamol. While the magnitude of the observed effect may result in sub-therapeutic plasma concentrations of lamotrigine in some patients, the clinical significance of our findings is not clear. An increase in seizures was reported for nine of 12 pregnant women receiving lamotrigine monotherapy. In these patients, the ratio of lamotrigine dose to plasma concentration was reduced by about 40%, compared with the ratio prior to pregnancy [20]. Frequency of seizures was increased by 38% among 69 pregnant women receiving lamotrigine monotherapy. Increase in seizure frequency appeared to be associated with a more than 35% reduction of anti-epileptic drug concentrations [21]. A nested case–control study within a population of epileptic patients receiving lamotrigine monotherapy could be used to detect seizure breakthrough as related to initiation of paracetamol therapy.

As the UDP glucuronosyltransferase 1A4 enzyme catalyzes the N-glucuronidation of primary, secondary and tertiary amine substrates [22], it is clear that the potential of paracetamol to cause drug–drug interactions may not be limited to an interaction with lamotrigine. This enzyme contributes to the metabolism of a number of drugs for which it may be hypothesized that concomitant administration of paracetamol be of clinical relevance, notably the second generation antipsychotic olanzapine [23].

In conclusion, paracetamol statistically significantly induced steady-state lamotrigine glucuronidation, resulting in a 20% decrease in total systemic exposure and a 25% decrease in trough value of lamotrigine. The clinical significance of this is unclear. Patients with plasma concentrations of lamotrigine at the lower end of the therapeutic range may be susceptible to such an interaction, and treating physicians should be aware of this potential drug–drug interaction.

Conflicts of Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; T.B. Stage has held unrelated, paid lectures for Eisai, Orifarm, Novartis and Astellas-Pharma. All other authors declare no other relationships or activities that could appear to have influenced the submitted work.

Author contributions

PD conceived the principal study idea. PD, TBS, SG and PF designed the study. SG, TBS and PD conducted the study.

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